

## II. FORMAL MATTERS

### 1. Restriction

Although Applicants did not traverse the restriction requirement, the election of species was made only because it was required in the response (See page 5 of Applicants submission dated 15 December 2005). Moreover, the Examiner is reminded that upon the finding of an allowable generic claim, claims presently withdraw as a result of the election of species requirement should automatically be rejoined and allowed (MPEP § 803.02 & 821.04). Accordingly, it is believed that allowance of generic claims 7 and/or 14 should result in the immediate reconsideration and allowance of the respective (presently withdrawn) dependent claims 9-12 and 16-19.

### 2. Information Disclosure Statement

The Examiner is thanked for return of the signed PTO-Form 1449 indicating consideration of various references cited. Enclosed please find a new Information Disclosure Statement and payment of the appropriate fee. Please consider the various additional references.

## III. RESPONSE TO THE OFFICE ACTION REJECTIONS

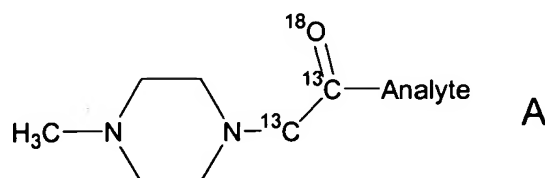
### 1. Rejection under 35 U.S.C. § 112, second paragraph

#### a) *The Law Of 35 U.S.C. § 112, Second Paragraph*

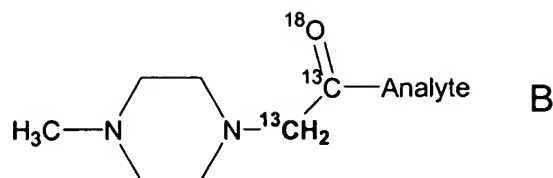
It is well settled that a claim is sufficiently definite for purposes of the second paragraph of 35 USC § 112, second paragraph if one of ordinary skill in the art would understand what is claimed when considered in light of the specification and the prior art. *Penda Corporation v. United States*, 29 Fed.Cl. 533, 554 (1993).

#### b) *Claims 7-8, 13-15 and 20 Are Sufficiently Clear*

While Applicants agree with the Examiner that, for example, formula A:

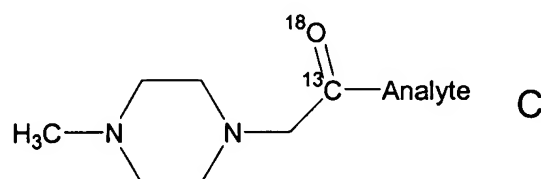


is the equivalent of formula B:

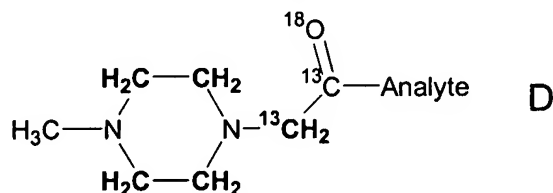


The operative question is whether or not one of skill in the art would appreciate this fact.

As the Examiner is certainly aware, if one weren't interested in highlighting the  $^{13}\text{C}$  in the structure, the methylene group of the compound could also be illustrated as it is in formula C:



In formula A, the  $^{13}\text{C}$  of the methylene group is specifically called out to distinguish its presence. As the Examiner is certainly aware, formulas A, B and C are consistent with well accepted chemical structural shorthand used by chemists to illustrate methylene groups. Certainly the Examiner understands this shorthand else he/she would also suggest that formula A be written as formula D:



as compared with formula B to thereby clarify all methylene groups of the heterocyclic ring.

In brief, in all cases the ordinary practitioner certainly would know that two hydrogen atoms are implied in all cases since carbon must have a valence of 4. Accordingly, it is believed that the structures of claims 7 and 14 are sufficiently clear for one of ordinary skill in the art to appreciate what is being claimed. Reconsideration and withdrawal of the rejection is respectfully requested.

## 2. Rejection under 35 U.S.C. § 103(a)

(a) *The Law Of 35 U.S.C. § 103(a)*

"A claimed invention is unpatentable if the differences between it and the prior art "are such that the subject matter as a whole (emphasis added) would have been obvious at the time the invention was made to a person of ordinary skill in the art." *In re Dembiczak*, 175 F.3d 994, 998, 50 U.S.P.Q.2d 1614, 1616 (Fed. Cir. 1999). In determining whether a claimed invention is obvious one must consider; 1) the scope and content of the prior art; 2) the level of skill in the prior art; 3) the differences between the claimed invention and the prior art; and 4) objective evidence of non-obviousness such as secondary factors. *Id.* (Also See: M.P.E.P. § 2141 and the Graham Factual Inquiry)

The PTO bears the burden under 35 U.S.C. § 103 to establish an un rebutted *prima facie* case of obviousness. *In re Rouffet*, 149 F.3d 1350, 1355, 47 U.S.P.Q.2d 1453, 1455 (Fed. Cir. 1998). To satisfy its burden, the PTO must show some objective teaching in the prior art or that knowledge generally available in the art **would lead the ordinary practitioner to combine relevant teaching.** *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). Both suggestion and reasonable expectation of success must be found in the prior art **and not in Applicant's disclosure.** *In re Vaack*, 947 F.2d 448, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). In whatever form, that showing must be **clear and particular.** *Winner International Royalty v. Wang*, 202 F.3d 1340, 1348-1349, 53 U.S.P.Q.2d 1580, 1587 (Fed. Cir. 2000).

An Examiner's cursory statement unaccompanied by evidence or reasoning is entirely inadequate to support a rejection. *In re Sichert*, 566 F.2d 1154, 1164, 196 U.S.P.Q. 209, 217 (C.C.P.A., 1977). A rejection based on section 103 must be based in fact that is not aided by hindsight. *In re Warner*, 54 C.C.P.A. 1628, 1635, 379 F.2d 1011, 1017, 154 U.S.P.Q. 173, 178 (C.C.P.A., 1967). **The PTO may not resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in its factual basis for a rejection.** *Id.* Doubts as the factual basis for a rejection must be resolved in favor of the Applicant since it is the PTO's burden to establish a *prima facie* case of obviousness. *Id.* In the absence of a proper *prima facie* case of obviousness, an Applicant is entitled to a patent. *In re Rouffet*, 149 F.3d 1350, 1355, 47 U.S.P.Q.2d 1453, 1455 (Fed. Cir. 1998). To overcome a claimed *prima facie* case of obviousness, an Applicant can either show that the *prima facie* case of obviousness is insufficient **because it relies on incorrect factual**

**predicates** or otherwise present secondary evidence of non-obviousness. *In re Rouffet*, 149 F.3d 1350, 1355, 47 U.S.P.Q.2d 1453, 1455 (Fed. Cir. 1998).

(b) *The Combined References Do Not Present A Prima Facie Case For Obviousness*

At pages 3-4 of the present Office Action, claims 7-8, 13-15 and 20 are rejected under 35 U.S.C. § 103 as being unpatentable over Lerchen (US 2005/0049406 in view of Shetty et al. (Biomed Mass Spectrom, 1983). Applicants respectfully traverse this rejection.

(i) A Premise Of The Argument Is Incorrect

At the bottom of page 3, the Office Action states: "*Lerchen et al. teach a mixture comprising fragment ions derived by fragmentation of the **same analyte labeled with two or more different isobaric labels**, wherein ions of the labeled analytes were selected for fragmentation and further analysis in a tandem mass spectrometer (e.g. claims and [0590]-[0591], [0612]-0617]).*" (emphasis added in bold, OA at page 3) It is respectfully submitted that Lerchen et al. does not teach analytes labeled with isobaric labels (labels of the same "nominal gross mass") but rather teach the very different concept of analytes labeled with mass differential labels (i.e. labels of distinct mass difference).

At page 5 of Applicants' specification isobar is defined as follows: "*As used herein, isobars are structurally and chemically indistinguishable compounds (except for isotopic content and/or distribution) of the **same nominal gross mass**.*" (Emphasis added in bold; Specification at page 5, lines 12-13) Examples of isobars that can be used as, or used to prepare, labeling reagents are illustrated in Figure 5A (e.g. compounds that produce the fragment ions (e.g. signature ions) 114, 115, 116 and 117 when fragmented in a mass spectrometer but which all have the same "nominal gross mass" prior to fragmentation in the mass spectrometer; See also Figures 5B and 5C). As discussed in the specification and examples, the unique isobaric labeling reagents described by Applicants produce labeled analytes of same "nominal gross mass" but which show their distinctive mass properties only after fragmentation (c.f. page 20, line 10 to page 24, line 11 of Applicants' specification).

By comparison, Lerchen et al. teach sets of mass labeling reagents wherein each labeling reagent of the set comprises a uniquely different mass such that like analytes

labeled with different labeling reagents of a set all comprise different masses.<sup>1</sup> For example, at paragraph [0617], Lerchen et al. state:

*"FIG 2 shows the ion traces for four differentially labeled variants of the peptide LQGIVSWGSGCAQD from Trypsinogen. From the top to the bottom, the traces relate to the peptide which has been labeled by the affinity tags 0, 5, 11 and 17 [See paragraphs [0599], [0600], [0601], [0602] and Examples 38-41 for structures] isotope labels. It is not possible to measure any retention differences between variants. FIG. 3 shows the appurtenant MS spectrum, which contains a quadruplet of almost equally intense signals. The identity of the peptide was confirmed by means of MS/MS analysis."*

(Clarification added in bracket; Lerchen et al. at para. [0617])

From the foregoing, it is clear that Lerchen et al. teach mass differential labels that produce labeled analytes of different mass (e.g. 0, 5, 11 and 17 mass units different). Accordingly, Lerchen does not teach the asserted element of: *"..same analyte labeled with two or more different isobaric labels..."* as asserted in the Office Action. Since the combined references don't teach all the elements/limitations of the claimed subject matter, there can be no *prima facie* case for obviousness. Thus, it is respectfully submitted that the rejection is defective for at least this reason.

(ii) Neither Shetty et al. nor Lerchen et al. Teach Relevant Labels

The present Office Action states: *"The adjustment of particular conventional working conditions (e.g. isotopically labeling the piperazine, selecting the linker to the analyte) is deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan. (See paragraphs [0020], [0038]-[0058]"* (OA at page 4). Respectfully,

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<sup>1</sup> At paragraph 3, Lerchen et al., in describing the ICAT technology that their invention follows, state: *"The method is based on each of two or more protein mixtures, which are to be compared and which have been obtained in different cell states, being reacted with an affinity tag or a different isotope coding. After that, the protein mixes are combined, where appropriate fractionated or treated proteolytically and purified by affinity chromatography. After the bound fragments have been eluted, the eluates are analyzed by a combination of liquid chromatography and mass spectrometry (LC-MS). Pairs of groups of peptides which are labeled with affinity tags which only differ in the isotope coding are chemically identical and are eluted virtually simultaneously in the HPLC; however, they differ in the mass spectrometer by the respective molecular weight differences due to the affinity labels having different isotope patterns."* (Emphasis added in bold – Lerchen et al. at paragraph 3)

because The Office may not resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in its factual basis for a rejection, this statement is strong evidence that neither reference indeed teaches the ordinary practitioner how to prepare the specific labeling reagents used to label the labeled analytes illustrated in claims 7 and 14.

Assuming arguendo that the particular arrangement of heavy atom isotopes is simply a "*matter of judicious selection*"<sup>2</sup>, neither reference teaches labeling reagents or labeled analytes of the particular structure illustrated in claims 7 and 14. In particular, while both references teach labels possessing a piperazine ring, neither teaches a N-methyl piperazine ring that is N-alkylated with an acetic acid moiety to which the analyte can be linked through the carbonyl carbon of said acetic acid moiety. Since The Office cannot resort to speculation and assumptions to provide elements/limitations of a *prima facie* case for obviousness, it is respectfully submitted that the rejection is defective for at least this reason.

(iii) Summary

For at least the reasons stated, it is believed that the asserted *prima facie* case for obviousness is deficient. Reconsideration of claims 7-8, 13-15 and 20 and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

**3. Rejections for Double Patenting**

At pages 5-6 of the present Office Action various claims are provisionally rejected under the judicially created doctrine of double patenting. It is respectfully submitted that all the patent applications remain pending and not allowed at this time, claims of one or more of the applications can be amended and/or canceled. Accordingly, this provisional rejection should be held in abeyance until such time as this application contains allowable subject matter or in the alternative until this application is determined to have otherwise allowable subject matter that conflicts with pending claims of the other patent

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<sup>2</sup> Which it is not since neither reference teaches isobaric labeling reagents and accordingly there is no basis for the ordinary practitioner to select starting materials that produce labeling reagents comprising a distribution of heavy atoms wherein all the labeling reagents have the same "nominal gross mass".

application(s). At such time, Applicants can reconsider the requirement for a terminal disclaimer or cancel the offending claims in one or more patent applications.

#### IV. SUMMARY

But for the provisional double patenting rejections, it is believed that this response addresses all the issues raised in the present Action and the application is in ready condition for allowance. In consideration of the preceding remarks, Applicants hereby respectfully request reconsideration of all pending claims and an indication of the allowability (but for resolution of any double patenting concerns) of claims 7-20 with the next Office communication.

#### V. INTERVIEW

If the Examiner believes a telephonic or personal interview would advance the prosecution of the subject application, the Examiner is invited to contact attorney Gildea during business hours at the telephone or facsimile numbers listed below.

#### VI. FEES

A new IDS and authorization to deduct the appropriate fee from Deposit Account 01-2213 for consideration of said IDS is being submitted herewith. Because this response is being filed within the shorted statutory period for response, it is believed that no fee is required for consideration of this response by the Office. If however, The Office determines that any fee is properly due for its consideration of this paper, authorization is hereby granted to charge any required fee associated with the filing or proper consideration of this paper to Deposit Account 01-2213 (Invoice No. BP0309US-CP1).

VII. CORRESPONDENCE/CUSTOMER NUMBER

Please send all correspondence pertaining to this document to:

Brian D. Gildea, Esq.  
Applied Biosystems  
500 Old Connecticut Path  
Framingham, MA 01701  
Telephone: 508-383-7632  
Fax: 508-383-7468  
Email: brian.gildea@appliedbiosystems.com

IF NOT ALREADY DONE, PLEASE ASSOCIATE THIS CASE WITH CUSTOMER  
NUMBER

**23544**

Respectfully submitted  
on behalf of Applicants,

June 8, 2006  
Date

Brian D. Gildea  
Brian D. Gildea, Esq.; Reg. No. 39,995